Claims 1-3, 5-35, 37-46 and 69-73 are pending. Claims 1, 5, 8, 13, 20, 22, 25, 32, 34, 39, 43 and 45 are amended. Claim 4 is cancelled without prejudice or disclaimer. Claim 1 is amended to incorporate the limitations of Claim Claims 5 and 13, which depended from cancelled Claim 4, are amended to depend from Claims 1 and 3, respectively. Claim 5 is also amended to particularly point out and distinctly claim the subject matter herein. Basis is found, e.g., at page 5, lines 1-4 of the specification, and at page 10, lines 23-26 of the specification. Claims 8, 20, 22, 25, 32, 39, 43 and 45 are re-written as independent claims that incorporate the elements of cancelled Claim 1. Claim 34 is amended to correct a minor grammatical error. Basis for the amended claims lies in the claims as originally filed. No new matter is added.

REQUEST FOR CLARIFICATION OF THE REQUIREMENT FOR RESTRICTION AND ELECTION OF SPECIES

A Requirement for Restriction and Election of Species (hereinafter, "Requirement for Restriction") was set forth in connection with the above-captioned application on September 11, 2001. In the Response to the Requirement for Restriction filed November 21, 2001, Applicant elected, without traverse, claims 1-35, 37-46 and 69-73, drawn to nucleic acid molecules, vectors, host cells and fusion proteins. In addition, responsive to the Election of Species requirement, Applicant elected "estrogen receptor" as the nuclear hormone receptor subtype for searching purposes.

The pending claims as amended are drawn to the generic concept set forth in former Claim 1, namely, a fusion protein that is a ligand activated transcriptional regulator comprising a nucleotide binding domain containing modular zinc-finger peptide units operatively linked to a ligand binding domain derived from an intracellular receptor.

Although, in the instant Office Action, the Examiner appears to have examined the claims as being drawn to the generic concept set forth in claim 1, whose elements were further specified in the dependent claims, the Examiner states that we have elected the Claims 1-35, 37-46 and 69-73 **as being drawn to a single nucleotide sequence, namely, SEQ ID. NO. 1.**

As discussed below, Applicant respectfully submits that if the Examiner indeed intended that the claims be restricted to a single nucleotide sequence, then such a restriction would be improper as applied to the instant claims. Further, as discussed below, restriction to a single sequence is inconsistent with the rejections set forth in the instant Office Action, all of which are directed to the generic structural and functional limitations of the claims and not to a particular sequence. Accordingly, because (i) if the Examiner has restricted the pending claims to a single sequence, then the Requirement for Restriction would be improper in the instant context; and (ii) the Examiner's apparent restriction of the claims to a single sequence is inconsistent with his examination of the claims as being drawn to a generic concept and not to a particular sequence, Applicant requests clarification of the nature of the Requirement for Restriction set forth on September 11, 2001, in connection with the instant application.

The claims are directed to fusion proteins that are ligand activated transcriptional regulators, which include a modified ligand binding domain. This is a generic product and a variety of components can be used. Absent a finding of a art that describes a species of such construct, there is no reason to limit it to a single sequence of nucleic acids. Countless examples of each component of the fusion protein are known to those of skill in the art. It is the instant application that teaches a construct that contains such components. In view of the instant disclosure, one of skill in the art, can readily identify the components and prepare fusion proteins that contain the requisit elements. These claims do not fall under the rules that govern the examination of applications directed to nucleic acid molecules. The searchable aspect is not the specific sequences but the fusion as a fusion of particular functional elements.

Inconsistencies in setting forth the nature of the Requirement for Restriction and El ction of Species

Applicant respectfully submits that it does not make sense to have dependent claims drawn to fusion proteins that are variants of a generic claim, where the generic claim is a specific molecule having a particular sequence (*i.e.*, SEQ ID NO. 1). Moreover, several of the rejections set forth in the instant Office

Action do not make sense if the generic claim is drawn to SEQ ID NO. 1. For example, the Examiner has rejected former Claim 1 under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,217,867 (Evans *et al.*), which allegedly discloses fusion polypeptides containing a zinc-finger domain from the thyroid hormone receptor fused with the transactivation domain of the glucocorticoid receptor. Without conceding the propriety of the rejection as directed against the generic concept set forth in Claim 1, if Claim 1 is drawn to SEQ ID NO. 1, which is the nucleic acid sequence encoding a fusion protein in which the estrogen receptor ligand binding domain is fused with a zinc finger polypeptide, then such a claim cannot be anticipated by a fusion protein whose components are domains of the glucocorticoid and thyroid receptors.

Also, as discussed below, the Election of Species requirement is rendered both meaningless and improper if it was intended that the claims be restricted to a single nucleic acid sequence.

Impropriety of the Requirement for Restriction and Election of Species if the claims were intended to be restricted to a single sequence

In addition to the inconsistencies noted above that make the nature of the Requirement for Restriction as set forth unclear, restriction of the claims to a single sequence, if such was intended, is improper in the instant context. Restrictions to single nucleotide sequences are discussed in §803.04 of the Manual of Patent Examining Procedure (MPEP). According to MPEP §803.04, claims drawn to nucleotide sequences encoding different proteins are deemed properly restrictable, although the Commissioner has decided *sua sponte* to partially waive this requirement for a reasonable number (usually, ten) of patentably distinct sequences. The restriction of nucleotide sequences applies to "applications **claiming** more than ten [usually] individual independent and distinct nucleotide sequences" (MPEP §803.04; emphasis added).

The generic concept set forth in the instant application is not directed to particular nucleic acid or protein sequences. Claim 1 is a generic claim to a fusion protein with specified structural and functional limitations. SEQ ID NO. 1 is an

exemplary molecule having the structural and functional elements of the generic concept set forth in Claim 1.

The structural and functional elements set forth in the generic claim can be searched by virtue of their properties, *e.g.*, ligand-binding domains of intracellular receptors and zinc finger proteins. By requiring restriction to a single sequence, the Requirement for Restriction, without citing any art, is urging that a fusion protein with components having the structural and functional properties as claimed is not patentable unless it is drawn to a particular fusion protein sequence. The Requirement for Restriction provides no evidence of record that the claimed fusion protein is only patentable as to particular sequences, nor are there any other reasons set forth for requiring restriction of the generic claim to particular nucleic acid sequences.

Moreover, if the Examiner considers the claims as being drawn to a single nucleotide sequence, the restriction to SEQ ID. NO. 1, which contains a zinc finger peptide sequence linked to an estrogen receptor ligand binding domain, would render election of the estrogen receptor in response to the Election of Species requirement meaningless. The instant claims can only be restricted to the designated species, *i.e.*, estrogen receptor, if no generic claim is deemed allowable. If a generic claim is ultimately allowed, then the additional claims directed to specific elements within each category, written in dependent form or otherwise including all the limitations of the allowed generic claim(s), will necessarily be allowed. In the Requirement for Restriction, the Examiner has restricted the generic claim to a fusion protein in which the intracellular receptor is the elected species, *i.e.*, the estrogen receptor (the sequence of the intracellular receptor set forth in SEQ ID NO. 1), without making any determinations as to allowability of the generic claim. Therefore, by restricting the generic claim to a particular sequence, *i.e.*, SEQ ID NO. 1, the Election of Species requirement is meaningless and improper.

In light of the above, Applicant requests clarification of the Requirement for Restriction as set forth in the instant application.

OBJECTION TO CLAIMS 11 AND 25

Claims 11 and 25 are objected to as being drawn to non-elected subject matter. With respect to Claim 25, this objection is respectfully traversed because restriction of the generic claim to a single sequence in the instant context is improper, as discussed above. Accordingly, Claim 25 as amended retains SEQ ID NOS. 1-18 pending clarification, discussed above, as to the nature of the Requirement for Restriction and Election of Species.

Claim 11 is drawn to the fusion protein of claim 1, wherein the intracellular receptor is a nuclear hormone receptor selected from the group consisting of estrogen receptors, progesterone receptors, glucocorticoid-α receptors, glucocorticoid-β receptors, mineralocorticoid receptors, androgen receptors, thyroid hormone receptors, retinoic acid receptors, retinoid X receptors, Vitamin D receptors, COUP-TF receptors, ecdysone receptors, Nurr-I receptors and orphan receptors. This claim can only be restricted to the elected species if the generic claim from which it depends is deemed unpatentable. In the instant Office Action, the Examiner has rejected the generic claim (former Claim 1) as being unpatentable because it is allegedly anticipated by U.S. Patent No. 5,217,867 (Evans *et al.*), which allegedly discloses fusion polypeptides containing a zinc-finger domain from the thyroid hormone receptor fused with the transactivation domain of the glucocorticoid receptor. As discussed below, Applicant requests reconsideration and removal of the anticipation rejection in light of the amendments and remarks herein. Therefore, the language of Claim 11 retains the species set forth in the claim, pending a determination as to the allowability of the generic claims as amended.

THE REJECTION OF CLAIMS 9, 13, 15, 16, 17, 18, 19 AND 39-46 UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Enablement Rejection

Claims 9, 13, 15, 16, 17, 18 and 19 are rejected under 35 U.S.C. § 112, first paragraph because it is alleged that the specification, while being enabling for for a substantially purified polypeptide comprising an amino acid sequence set forth in SEQ ID NO. 1, does not reasonably provide enablement for a protein variant of SEQ ID NO. 1. It is further alleged that the rejected claims are overly

broad in their recitation of "variant" because while the specification discloses variants of the protein as having mutations, truncations or insertions made to SEQ ID NO. 1, no actual or prophetic examples on expected performance parameters of any of the possible muteins of SEQ ID NO. 1 are allegedly disclosed. Furthermore, the Examiner alleges that the fusion proteins exemplified provide as to generation of the "myriad of polypeptide species" encompassed by the claim that will retain the characteristics of a zinc-finger nucleotide binding polypeptide. The Examiner cites references (Miyakama *et al.*, *Proc. Natl. Acad. Sci. USA* 90:10056-10060 (1993); Voet, *Biochemistry*, John Wiley & Sons, (1990)), for the proposition that even single amino acid changes can have dramatic effects on a protein's function, structure or architecture. The Examiner concludes that given the breadth of the cited claims in light of the predictability of the art as determined by the number of working examples, the level of skill in the art, and the guidance provided in the specification and the art of record, it would require undue experimentation for one of skill in the art to make and use the claimed subject matter.

Claims 39-46 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement because it is alleged that the specification does not adequately teach how to effectively treat any disease or reach any therapeutic endpoint in humans by administering a composition containing a fusion protein and a regulatable expression cassette containing at least one response element recognized by the nucleic acid binding domain of the fusion protein. The Examiner cites Eck and Wilson, *"Gene-Based Therapy"*, Ch. 5, pp. 77-101, Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, 9th ed. (1996), for the proposition that numerous factors complicate *in vivo* gene therapy with respect to predictably achieving levels and duration of gene expression that have not shown to be overcome by routine experimentation, including the fate of the DNA vector, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level and stability of the mRNA produced, the level and stability of protein produced, the fate of the protein within the cell, once produced, and the disease

and/or host being treated. The Examiner concludes that in light of the state of the art for gene therapy, and the lack of predictability thereof, the specification allegedly fails to provide guidance for any of the above parameters for *in vivo* gene expression, nor, allegedly, does the specification provide a clear correlation for carrying out gene therapy with regard to obtaining a particular therapeutic effect in a particular disease or disorder by administering the claimed composition.

This rejection is respectfully traversed.

Relevant law

To satisfy the enablement requirement of 35 U.S.C § 112, first paragraph, the specification must teach one of skill in the art to make and use the invention without undue experimentation. Atlas Powder Co. v. E.I. DuPont de Nemours, 750 F.2d 1569, 224 USPQ 409 (1984). This requirement can be met by providing sufficient disclosure, either through illustrative examples or terminology, to teach one of skill in the art how to make and how to use the claimed subject matter without undue experimentation. This clause does not require "a specific example of everything *within the scope* of a broad claim." In re Anderson, 176 USPQ 331, at 333 (CCPA 1973), emphasis in original. Rather, the requirements of § 112, first paragraph "can be fulfilled by the use of illustrative examples **or** by broad terminology." In re Marzocci et al., 469 USPQ 367 (CCPA 1971)(emphasis added).

Further, because "it is manifestly impracticable for an applicant who discloses a generic invention to give an example of every species falling within it, or even to name every such species, it is sufficient if the disclosure teaches those skilled in the art what the invention is and how to practice it." In re Grimme, Keil and Schmitz, 124 USPQ 449, 502 (CCPA 1960). Thus, there is no doubt that a patentee's invention may be broader than the particular embodiment shown in the specification. A patentee not only is entitled to narrow claims particularly directed to the preferred embodiment, but also to broad claims that define the invention without a reference to specific instrumentalities. Smith v. Snow, 294 U.S. 1, 11, 24 USPQ 26, 30 (1935).

Thus, there is no requirement for disclosure of every species within a genus. Applicant is entitled to claims are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has disclosed.

The inquiry with respect to scope of enablement under 35 U.S.C. §112, first paragraph, is whether it would require undue experimentation to make and use the claimed invention. A considerable amount of experimentation is permissible, particularly if it is routine experimentation. The amount of experimentation that is permissible depends upon a number of factors, which include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, and the breadth of the claims. Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986); see also In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988).

Analysis

Claims 9, 13, 15, 16, 17, 18, 19

Scope of the claims

The claims are directed to fusion proteins comprising a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, which may further comprise an operatively linked transcription regulating domain. The nucleotide binding domain set forth in the claims is a polydactyl zinc-finger peptide or modular portion thereof that is assembled from one or more modular units wherein each modular unit specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides. The ligand binding domain may be derived from a nuclear hormone receptor that has been modified to change its selectivity compared to the native hormone receptor. The claims further specify that in the claimed fusion proteins, the zinc-finger peptide can contain a zinc finger or a variant thereof that specifically binds to a targeted nucleic acid molecule, that the hormone receptor may be a progesterone or estrogen receptor variant that has selectivity and sensitivity for endogenous and exogenous ligands that differ from

its native ligands, and the transcription regulating domain may be a variant, derivative, multimer or other combination of known transcription regulating domains. The classes of molecules belonging to each of the domains of the fusion proteins claimed in the instant application are well characterized in the specification and are known to those of skill in the art, as are the modifications that render variants that retain the structural and functional characteristics of each of these domains. Contrary to the Examiner's assertion, the specification provides the common structural and functional features that characterize each domain, and the specification further provides specific guidance, with several examples, as to the preparation of variants that possess the requisite structural and functional characteristics of the instantly claimed fusion proteins.

The specification provides the types of modifications that would constitute variants that are within the scope of the claims, as well as means by which to identify such variants. While the Examiner's suggestion that single amino acid substitutions may result in dramatic structural and functional changes in a protein is not disputed, the instant specification describes in great detail the selection of variants having the structural and functional limitations of the generic claim, and such selection of variants of each domain as provided in the specification is known to those of skill in the art. Therefore, the metes and bounds of the variant proteins as instantly claimed are clear.

It would not require undue experimentation to select the variant domains of the fusion proteins that are within the scope of the instant claims, given what is known to those of skill in the art and is enabled by the specification regarding the structural and functional characterization of each of domains. Furthermore, it would not require undue experimentation to prepare the fusion proteins as claimed.

Teachings of the specification

As discussed above, the specification provides the types of modifications that would constitute variants that are within the scope of the claims, as well as means by which to identify such variants. The specification describes that variants of the ligand binding domain have altered selectivity and sensitivity for endogenous or exogenous ligands, such as a therapeutic ligand, and the specification teaches

how ligand binding domains, well characterized and known to those of skill in the art, may be modified to alter ligand sensitivity. The specification also teaches the types of sequence variants that retain the properties of a zinc finger binding domain or a transcription regulation domain, and the selection of these variants.

For example, page 32, line 7 to page 33, line 11 of the specification provides methods, known to those of skill in the art, to prepare and characterize variants of the ligand binding domain, including specific changes that will provide altered endogenous or exogenous ligand specificity as desired. Page 33, line 12 to page 50, line 2 of the specification provides in exquisite detail and incorporates by reference what was known to those of skill in the art at the time of filing of the application concerning zinc finger proteins, the modular nature of zinc finger proteins wherein each zinc finger specifically recognizes a 3 nucleotide sequence, the types of zinc finger proteins, specific changes that provide variant zinc finger peptides that retain the characteristics of recognizing zinc finger DNA binding motifs, how to construct, isolate or synthesize such variants, and how to screen for such variants. Page 50, line 3 to page 52, line 5 of the specification discloses known transcriptional regulatory domains and selection and modifications thereof. At, for example, page 31, line 6, to page 32, line 6, the specification teaches how to construct the claimed fusion proteins from the various domains and their variants. In addition, numerous working examples, discussed below, are provided throughout the specification, as are exemplary fusion proteins, encoded by SEQ ID NOS. 1-18.

The teachings of the specification, when taken in conjunction with what is known to one of skill in the art, are such that it would requires no undue experimentation to (i) select variant domains having the structural and functional characteristics of ligand binding domains, zinc finger peptide DNA binding domains, or transcription regulation domains domain that recognizes a specific growth factor or cytokine receptor expressed on a target cell; (ii) isolate and screen the variant domains for their structural and functional limitations as claimed; (iii) construct the fusion proteins as claimed; and (iv) screen for the DNA binding specificity and transcription regulation activity of the constructed fusion proteins.

Level of skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents made of record in this application address a highly skilled audience and further evidence the high level of skill in this art.

Knowledge of those of skill in the art

At the time of the effective filing date of this application and before, the skilled artisan knew the biochemical and structural characteristics and properties of receptors and proteins forming the domains of the instantly claimed fusion proteins. Further, there was a large body of literature, set forth below and incorporated in the instant specification by reference, that was directed to the identity, structure and function of each of the domains of the claimed fusion proteins. Moreover, the recognition domains and/or ligands through which each of the domains elicit their effects were well known. Also known to those of skill in the art were methods of selecting, modifying and screening for each of the domain variants to obtain the structural and functional properties of ligand binding, target sequence recognition and binding, and transcription regulation that are desired.

For instance, means to modify and test the specificity of hormone receptor ligand binding domains and to identify ligands therefor were known (see, U.S. Patent No. 5,874,534; U.S. Patent No. 5,935,934; and International PCT application No. 98/18925, which is based on U.S. provisional application Serial No. 60/029,964; International PCT application No. 96/40911, which is based on U.S. application Serial No. 08/479,913). Exemplary ligand binding domain modifications that lead to desired properties, such as preferential interaction with non-natural ligands, were also known to those of skill in the art (see, *e.g.*, U.S. Patent No. 5,874,534; U.S. Patent No. 5,935,934; U.S. Patent No. 5,364,791; and International PCT application No. 98/18925, which is based on U.S. provisional application Serial No. 60/029,964; International PCT application No. 96/40911, which is based on U.S. application Serial No. 08/479,913l) and references cited therein.

For example, methods and rules for preparation and selection of zinc fingers based upon the C2H2 class of zinc fingers with unique specificity were known (see, *e.g.*, International PCT application No. WO 98/54311 and International PCT application No. 95/19431; see, also U.S. Patent No. 5,789,538; Beerli *et al.* (1999) *Proc. Natl. Acad. Sci. U.S.A. 96*:2758-2763; Beerli *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A. 95*:14628-14633; see, also U.S. application Serial No. 09/173,941, filed 16 October, 1998, published as International PCT application No. WO 00/23464). It was also known that zinc finger variants can be prepared by identifying a zinc finger or modular unit thereof, creating an expression library, such as a phage display library (see, *e.g.*, International PCT application No. WO 98/54311, Barbas *et al.* (1991) *Methods 2*:119; Barbas *et al.* (1992) *Proc. Natl. Acad. Sci. U.S.A. 89*:4457), encoding polypeptide variants of the zinc finger or modular unit therof, expressing the library in a host and screening for variant peptides having a desired specificity.

It was known to those of skill in the art that a zinc finger-nucleotide binding peptide domain contains a unique heptamer (contiguous sequence of 7 amino acid residues) within the α-helical domain of the polypeptide, which heptameric sequence determines binding specificity to a target necleotide. It was also known that three zinc finger domains can bind 9 bp of contiguous DNA sequence (Pavletich *et al.* (1991) *Science 252*:809-817; Swirnoff *et al.* (1995) *Mol. Cell. Biol. 15*:2275-2287). Furthermore, it was known that while recognition of 9 bp of sequence is insufficient to specify a unique site in a complex genome, proteins containing six zinc finger domains can specify 18-bp recognition (Liu *et al.* (1997) *Proc. Natl. Acad. Sci. USA 94*:5525-5530). An 18-bp address made up of modular units was known to be of sufficient complexity to specify a single site within all known genomes (see, published International PCT application No. WO 98/54311). Rules for constructing Zinc finger arrays that bind to a particular DNA sequence were known (see, *e.g.*, International PCT application No. WO 98/54311, which is based on U.S. application Serial No. 08/863,813; International PCT application No. 95/19431, which is based on U.S. application Serial Nos. 08/183,119 and 08/312,604).

The murine Cys_2-His_2 zinc finger protein Zif268 had been used for construction of phage display libraries (Wu *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A. 92*:344-348). Zif268 was a structurally well characterized zinc-finger proteins (Pavletich, *et al.* (1991) *Science 252*:809-817; Elrod-Erickson *et al.* (1996) *Structure 4*:1171-1180; Swirnoff *et al.* (1995) *Mol. Cell. Biol. 15*:2275-2287). DNA recognition in each of the three zinc finger domains of this protein was known to be mediated by residues in the N-terminus of the α-helix contacting primarily three nucleotides on a single strand of the DNA. The operator binding site for this three finger protein was identified as 5'-GCGTGGGCG-'3 (finger-2 subsite is underlined). Structural studies of Zif268 and other related zinc finger-DNA complexes had shown that residues from primarily three positions on the α-helix, -1, 3, and 6, are involved in specific base contacts.

Also known to those of skill in the art at the time of filing of the instant application was the construction of highly diverse zinc finger libraries in the phage display vector pComb3H (Barbas *et al.* (1991) *Proc. Natl. Acad. Sci. USA 88*:7978-7982; Rader *et al.* (1997) *Curr. Opin. Biotechnol. 8*:503-508). Both libraries involved randomization of residues within the α-helix of finger 2 of C7, a variant of Zif268 (Wu *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A. 92*:344-348). Techniques for modifying zinc finger peptides were known (see, *e.g.*, U.S. Patent No. 5,789,538), as were binding site selection methods (Thiesen *et al.* (1990) *Nucleic Acids Research,* 18:3203, 1990).

Transcriptional regulatory domains were also known to those of skill in the art, as were transcriptional repressors and their structural and functional characteristics (Sgouras *et al.* (1995) *EMBO J. 14*:4781-4793, ERD domain mediating the antagonistic effect of ERF on the activity of transcription factors of the *ets* family; Margolin *et al.* (1994) *Proc. Natl. Acad. Sci. USA 91*:4509-4513; Pengue *et al.* (1996) *Proc. Natl. Acad. Sci. USA 93*:1015-1020; Friedman *et al.* (1996) *Genes & Dev. 10*:2067-2078, KRAB repressor domain; Ayer *et al.* (1996) *Mol. Cell. Biol. 16*:5772-5781, repression by histone deacetylation).

Pr senc of working exampl s

The specification provides numerous working examples and descriptions of the construction and expression of the claimed fusion proteins. Example 1 at page 67 of the specification describes in great detail the construction and testing of exemplary zinc finger domains. Example 1 shows how variants that specifically recognize the "GNN" target triplet nucleotide sequence of a zinc finger modular unit can be selected. Example 2 at page 84 provides the construction of fusion proteins containing zinc finger domains and transcriptional repressors and activators. Example 2 also shows regulation of *erbB-2* and *integrin β3* promoter activity using these exemplary constructs. Example 3 at page describes in great detail cell lines that are engineered to study specific binding interactions between the claimed bispecific fusion proteins and target antigens and/or costimulatory counter receptors. Further, Example 2 describes in great detail the construction and expression in yeast of the anti-ErbB2 - B7-2 bispecific fusion protein, and its structural characterization. Example 3 at page 87 of the specification provides the construction of fusion proteins using progesterone receptor variants, and Example 4 at page 89 of the specification demonstrates the same for estrogen receptor variants. Example 5 at page 97 of the specification provides the ligand dependent regulation of transgene expression by exemplary fusion proteins, and Examples 6-8 and 16-18 beginning at page 100 and page 119, respectively, of the specification provides exemplary structural characterizations and evaluations of the correlating regulatory activity of the individual domains and the fusion protein constructs. Example 14 at page 113 of the specification demonstrates how the estrogen receptor ligand binding domain may be modified to obtain variants with altered ligand selectivity.

Predictability

As is known to those of skill in the art (described above), the level of knowledge and skill in the construction, expression and assay of the claimed fusion proteins was so high as of the effective filing date that it would not have required undue experimentation by one of skill in the art to substitute a domain variant provided by the methods in the working examples and the publications incorporated herein by reference for the exemplified fusion proteins of the instant

application, nor would it have required undue experimentation to express or assay the fusion proteins wherein such substitutions have been made.

Conclusion

Therefore, in light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, and the breadth of the claims, it would not require undue experimentation for the skilled artisan to make and use the claimed bispecific fusion proteins.

Also, since the structural and functional characteristics of the various domain components of the instantly claimed fusion proteins are known, and since their effects can be determined by the standard methods extensively elucidated in the specification, it would be unfair and unduly limiting to require Applicant to limit these claims to a few exemplary sequences. To do so is contrary to the public policy upon which the U.S. patent laws are based. If applicant is required to limit the claims to only the exemplified fusion proteins, then those of skill in the art could by virtue of the teachings of this application readily practice what is claimed by substituting other ligand binding domains, zinc finger peptides or modular units thereof, and transcription regulation domains, but avoid infringing such limited claims. To permit that is simply not fair. The instant application exemplifies the means for isolation, modification and screening of domains having the structural and functional limitations as generically claimed, as well as the means for construction and expression of the fusion proteins, and *in vitro* and *in vivo* assays for their sequence specificity and regulatory activity. Having done so, it is now routine to for others to insert other ligand binding, zinc finger, and transcription regulatory domains into the exemplified fusion proteins. Those of skill in the art should not be permitted to make such minor modifications by substitution of a different host and avoid infringing such claims.

Claims 39-46

Scop of the Claims

Claims 39-46 are directed to combinations and compositions comprising a fusion protein containing a nucleotide binding domain operatively linked to a ligand binding domain that may further contain an operatively linked transcription regulating domain where the nucleotide binding domain is a polydactyl zinc finger peptide or a modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides and the fusion protein is a ligand activated transcriptional regulator, or a nucleic acid molecule comprising a sequence of nucleotides that encodes the fusion protein, and either (i) a regulatable expression cassette containing at least one response element recognized by the nucleic acid binding domain of the fusion protein and may also contain a gene encoding a therapeutic product; or (ii) a pharmaceutically acceptable excipient that is formulated for single dosage administration. All of the claims are directed to compositions and combinations that are based in specific elements, *i.e.*, a fusion protein, a regulatable expression cassette, a gene encoding a therapeutic product, and a pharmaceutically acceptable excipient.

The specification describes in extensive detail the preparation, characterization, and isolation of the claimed fusion proteins. The specification further provides details regarding the generation of expression cassettes containing genes encoding therapeutic products and response elements to which the nucleic acid binding domains of the claimed fusion proteins are bound. The specification further exemplifies introduction of such expression cassettes *in vitro* or *in vivo* using suitable delivery vectors, describes pharmaceutically acceptable excipients, and demonstrates *in vitro*, *in vivo* and *ex vivo* therapeutic regulation of gene expression using combinations or compositions containing exemplary fusion proteins and regulatable expression cassettes. As discussed below, numerous examples of particular fusion proteins regulating the *in vivo* and *in vitro* expression of genes encoded in exemplary expression cassettes are provided in the specification.

Applicant is entitled to claims that are commensurate in scope not only with what applicant has specifically exemplified, but commensurate in scope with that which one of skill in the art could obtain by virtue of that which the applicant has

disclosed. In the above-captioned application, Applicants disclose to the public fusion proteins and compositions/combinations thereof that are stably introduced into target cells and tissue, including cells and tissue of a host animal, and are demonstrated to be capable of binding to specific response elements and regulating the expression of exemplary therapeutic genes. The compositions and combinations disclosed in the application can be manipulated and used to regulate genes encoding a therapeutic product, in target cells and tissue, including target cells and tissue of a host animal, as is taught and specifically exemplified in the specification. Given the enormous level of structural and functional detail of the component domains of the claimed fusion proteins that is exemplified in the instant specification and is known to those of skill in the art, the compositions and combinations artificial provided in the subject application are uniquely suited for use as a versatile vehicle that can be tailored for the expression of desired therapeutic products in animals. Thus, it is respectfully submitted that Applicants' discovery is entitled to broad claim protection.

As taught in the above-captioned application, any methods known in the art pertaining to introduction of foreign genes carried in traditional, standard sources (such as genes harbored in expression vectors) into cells for any variety of purposes, e.g., protein production, protein modification, selection of desired protein variants, and gene therapy, may be applied in similar fashion to the introduction of the instantly claimed compositions and combinations into cells. As described and exemplified in great detail in the specification, the success of any particular method for introducing the compositions and combinations into cells can be ascertained by binding assays to detect sequence specificity of the fusion protein, and by changes in gene expression that are responsive to exposure of the cells to a ligand that specifically binds to the fusion protein. The application describes and demonstrates that once the regulatable cassette and fusion protein are generated and isolated and/or introduced into cells, then any known procedure that has previously been carried out with any heterologous gene from any source is applicable to utilization of the claimed compositions and combinations as regulators of gene expression.

It is therefore respectfully submitted that the instant claims are commensurate in scope with the discovery and its disclosure within the above-captioned application. It would be unfair and contrary to the Constitutional mandate set forth in Article, Section 8, to deprive Applicants of protection of the broad applications of discovery disclosed and described in exhaustive detail in the subject application.

As discussed below, the claims are commensurate in scope with the disclosure, which exemplifies particular embodiments within the scope of the claims and also teaches how one of skill in the art can obtain other embodiments within the scope of the claims. In particular, there is an enormous amount of guidance presented in the specification, there are numerous working examples, the level of skill in the art is high, and the state of the prior art at the time of filing of the application was such that a large amount of information was available concerning recombinant DNA techniques and procedures for the manipulation of DNA for the introduction of DNA encoding specific gene products into target cells and tissue, including the cells and tissue of a host animal, and expression of the encoded gene products in such cells and tissue. Therefore, it would not require undue experimentation for one of skill in the art to make and use the claimed subject matter.

Level of skill

The level of skill in this art is recognized to be high (see, *e.g.*, Ex parte Forman, 230 USPQ 546 (Bd. Pat. App. & Int'f 1986)). The numerous articles and patents relating to established procedures for nucleic acid manipulation, transfer and expression made of record in this application, which are authored and reviewed by those of skill in the art, further evidences the high degree of skill in this art.

Knowledge of those of skill in the art

At the time of filing of the application, a broad body of knowledge had

amassed in the area of molecular biology including many technical procedures covering the manipulation of DNA and recombinant DNA techniques. Numerous such procedures are referenced in the instant application, for example, as follows:

1) Genetic modification of a cell may be accomplished using one or more techniques well known in the gene therapy field (Human Gene Therapy, April 1994, Vol. 5, p. 543-563; Mulligan, R.C. 1993).

2) Dual component vectors and use for gene therapy are known (see, *e.g.*, Burcin *et al.* (1999) *Proc. Natl. Acad. Sci. USA 96*: 335-360, which describes an adenovirus vector fully deleted of viral backbone genes).

3) Requirements for efficient gene transfer using liposomes as a delivery vehicle include (1) encapsulation of the genes of interest at high efficiency while not compromising their biological activity; (2) preferential and substantial binding to a target cell in comparison to non-target cells; (3) delivery of the aqueous contents of the vesicle to the target cell cytoplasm at high efficiency; and (4) accurate and effective expression of genetic information (Mannino, *et al., Biotechniques*, 6:682, 1988). RNA, DNA and intact virions can be encapsulated within the aqueous liposome interior and be delivered to cells in a biologically active form (Fraley, *et al., Trends Biochem. Sci.*, 6:77, 1981).

4) The method for adenovirus production is described in detail, for example, in He *et al.* (1998) *Proc. Natl. Acad. Sci. U.S.A. 95*:2509-2514. Adenovirus vector construction is described in Gorziglia *et al.* (1996) *J. Virol. 70*:4173-4178.

5) It has previously been observed with fusion proteins containing an estrogen receptor ligand binding domain, that activity could be induced by use of not only the natural agonist estrogen (E2) but also synthetic anti-estrogens such as 4-OH tamoxifen (Littlewood *et al.* (1995) *Nucl. Acids Res. 23*:1686-1690; Danielian *et al.* (1993) *Mol. Endocrinol. 7*:234-240). The ability of the C7LBD fusion to be induced by 4-OH-tamoxifen was demonstrated.

6) In addition, numerous commercially available plasmids and other well established reagents such as lipids, retroviral vectors, to prepare suitable vectors to effect gene transfer, to manipulate DNA, to prepare DNA probes and plasmids, *etc.* are provided throughout the specification.

These references to several published protocols for DNA manipulation, recombinant DNA expression, and analysis thereof demonstrate the volume of information regarding tested and reliable procedures available at the time of filing of the instant application and thus evidence the advanced state of the art at the relevant time.

Presence of working examples

The specification provides numerous working examples and descriptions of the construction and delivery of the compositions and combinations. Example 2 at page 82 of the specification shows regulation of *erbB-2* and *integrin β3* (both therapeutic gene products as elaborated in the specification) by exemplary fusion constructs. Examples 4 and 19 at pages 89 and 122 of the specification, respectively, set forth in great detail the cloning strategies and the preparation of exemplary regulatable cassettes. Examples 5 and 6 beginning at page 97 of the specification provide the ligand dependent regulation of transgene expression in cells by exemplary fusion proteins, and Examples 6-8 and 16-18 beginning at page 100 and page 119, respectively, of the specification provides exemplary structural characterizations and evaluations of the correlating regulatory activity of the individual domains and the fusion protein constructs in response to endogeneous and exogenous ligands. Example 19 at page 122 of the specification demonstrates the in vivo and in vitro regulation of exemplary regulatable expression cassettes using exemplary fusion proteins constructed as set forth in the various working examples and delivered using adenoviral vectors.

In summary, the specification enables one of ordinary skill in the art to, by following the methods set forth therein, construct fusion proteins and regulatable cassettes, introduce them into cells, tissues, and/or animal hosts, and regulate the expression of exemplary genes encoding therapeutic products. By virtue of Applicant's detailed teachings of each of the components set forth in the claimed compositions and combinations, those of skill in the art are able, without undue experimentation, to make and use the claimed compositions and combinations and to combine their use with known recombinant DNA procedures, many of which are referenced in the specification, to achieve any number of particular outcomes,

including the introduction and long-term expression of nucleic acids encoding therapeutic products and regulatory fusion proteins as claimed in cells and tissues of host animals.

Predictability

As is known to those of skill in the art (described above), the level of knowledge and skill in the construction, expression and assay of the claimed compositions and combinations was so high as of the effective filing date that it would not have required undue experimentation by one of skill in the art to achieve the introduction and long-term expression of nucleic acids encoding therapeutic products and regulating fusion proteins as claimed in cells and tissues of host animals, substitute a component of the claimed compositions and combinations provided by the methods in the working examples and the publications incorporated by references, and express or assay the combinations and compositions wherein such substitutions have been made.

REBUTTAL TO EXAMINER'S COMMENTS REGARDING ECK AND WILSON ET AL.

The Examiner alleges that Eck and Wilson, cited in the instant Office Action, demonstrate that numerous factors complicate *in vivo* gene therapy with respect to predictably achieving levels and duration of gene expression that have not shown to be overcome by routine experimentation, including the fate of the DNA vector, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level and stability of the mRNA produced, the level and stability of protein produced, the fate of the protein within the cell, once produced, and the disease and/or host being treated. A significant portion of the grounds for the rejection of the claims under 35 U.S.C. § 112, first paragraph, is based on the alleged unpredictability of the art of gene therapy in general.

In response, **Applicant respectfully submits that the question of whether the instant claims satisfy the requirements of 35 U.S.C. § 112, first paragraph does not turn on the pr dictability/unpredictability of the art of g ne therapy**. The pending claims are directed to compositions and combinations containing a fusion

protein whose construction is set forth in great detail, and a regulatable cassette containing a response element that is recognized by the nucleotide binding domain of the fusion protein, also set forth in similar detail. **The claims are not directed to general methods of curing disease or to general methods of gene therapy per se.** Instead, the claims are directed to compositions and combinations containing specific components that, as discussed above, are elucidated in great detail in the form of descriptions throughout the specification and in working examples so that they may be optimized for particular applications in gene therapy. The claimed compositions and combinations are uniquely recognizable as being important tools for the regulation of gene expression.

A significant portion of the grounds for the rejection of the claims under 35 U.S.C. § 112, first paragraph, is based on the alleged unpredictability of the art of gene therapy in general. As explained above, however, the issue of whether the specific instant claims are enabled by the specification should not turn on the state of the art of gene therapy as generally discussed in the first two pages of the Office Action. Instead, the relevant question with regard to enablement of the subject matter of the instant claims is whether the particular steps and materials of the claimed methods are described in the specification in such a way as to enable one skilled in the art to make and use the subject matter **as claimed**.

The Examiner points to Eck and Wilson as an assessment of the state of the art of gene therapy at the time the instant invention was made, citing problems of impracticality and unpredictability such as the fate of the DNA vector, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level and stability of the mRNA produced, the level and stability of protein produced, the fate of the protein within the cell, once produced, and the disease and/or host being treated.

It is respectfully submitted that such a selective reading of Eck and Wilson, in which statements regarding the state of gene therapy in 1996 are taken out of context, has resulted in a mischaracterization of the reference that cannot validly be relied on to support an allegation of unpredictability of gene therapy. For

example, the abstract of Eck and Wilson mentions how gene therapy has overcome barriers of the former cellular inaccessibility of large proteins encoded by therapeutic genes. The article provides several examples of the progress made in developing delivery systems for gene therapy, its applications not only in inherited single-gene defects, but also in acquired illnesses such as cancer, cardiovascular and infectious diseases, and the continual advancement for strategies to introduce recombinant DNA into tissues in a selective manner.

Although Eck and Wilson acknowledge that gene transfer was not an established clinical treatment regime, it clearly had been demonstrated, *based on actual clinical trial data*, that therapeutically relevant genes could be transferred into human patients and be expressed within the patient in such a manner as to show biologic efficacy. Eck and Wilson further provides a summary of the studies demonstrating that transfer of genes to humans is feasible (see Table 5-1, pp. 80-81) and statistics concerning the numbers and outcomes of human gene transfer studies. Eck and Wilson concludes that human gene therapy, although still in its infancy, offers the possibility for "major advancements in the prevention and treatment of many diseases". They also conclude that as "increasing numbers of investigators address these issues, better reagents likely will emerge".

Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for a treatment-related area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. § 112, first paragraph, is not a consideration. The relevant standard is not that of an established, fully optimized, clinical course of treatment; rather, even in an *unpredictable* art, a patent application satisfies the requirements of 35 U.S.C. § 112, first paragraph, as long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. There is no requirement that a treatment method achieve a specified level of efficacy or efficiency in order to be considered "enabled" by the specification.

Contrary to the position set forth in the Office Action, Eck and Wilson's assessment of the state of the art of gene therapy is that therapeutic gene transfer to humans has been proven to be feasible, as borne out by successes in gene transfer clinical trials, and its accomplishments to date at the time of publication were impressive.

It appears that the Examiner, in asserting the unpredictability of the art of gene therapy, has equated "limitations" with "unpredictability." It is respectfully submitted that although methods of gene therapy may be associated with certain limitations and limited success, this does not establish the art as unpredictable. In fact, with respect to methods of gene therapy, the well-studied, -identified and -characterized limitations of the art, as determined through years of research and, as Eck and Wilson *et al.* report, several clinical trials, make the methods all the more predictable. The practitioner is well aware of the potential obstacles and clearly knows what he or she is up against in designing and carrying out such therapeutic methods. As such, it is respectfully submitted, that although the art of gene therapy may not have been a routine, clinical practice at the effective filing date of the subject application, it was not so unpredictable as to qualify as a major factor in the determination of whether the requirements of 35 U.S.C. § 112, first paragraph, are satisfied with respect to the instantly claimed subject matter.

Conclusion

Therefore, in light of the extensive teachings and examples in the specification, the high level of skill of those in this art, the knowledge of those of skill in the art, and the breadth of the claims, it would not require undue experimentation for the skilled artisan to make and use the claimed compositions and combinations.

Written Description Rejection

Claims 9, 13, 15, 16, 17, 18 and 19 are rejected under 35 U.S.C. §112,

first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed subject matter at the time the application was filed. Without addressing a particular claim, the Examiner alleges that "this" is a genus claim. The Examiner further alleges that the specification and claims are not sufficiently descriptive of the term "variant" as to indicate what distinguishing features (amino acid substitutions, deletions, additions and/or insertions) from others in the protein class fall within its scope. Furthermore, the Examiner alleges that the specification provides insufficient guidance as to the changes that may be made to distinguish compounds in the genus from others that are missing from the disclosure. The Examiner asserts that "no common structural attributes identify the members of the genus".
This rejection is respectfully traversed.

Relevant Law

The purpose behind the written description requirement is to ensure that the patent applicant had possessio of the claimed subject mater at the time of filing of the application In re Wertheim, 541 F.2d 257, 262, 191 USPQ 90, 96 (CCPA 1976). The manner in which the specification meets the requirement is not material; it may be met by either an express or an implicit disclosure.

35 U.S.C. §112 requires a written description of the invention. This requirement is distinct from and not coterminous with the enablement requirement:

> The purpose of the 'written description' requirement is broader than to merely explain how to 'make and use'; the applicant must also convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." Vas-Cath, Inc. v. Mahurkar, 935 F.2d at 1563-64, 19 USPQ2d at 1117 (emphasis in original).

The issue with respect to 35 U.S.C. §112, first paragraph, adequate written description has been stated as:

> [d]oes the specification convey clearly to those skilled in the art, to whom it is addressed, in any way, the information that appellants invented that specific compound [claimed embodiment] Vas-Cath, Inc. v. Mahurkar, at

1115, quoting In re Ruschig, 390 F.2d 1990, at 995-996, 154 USPQ 118 at 123 (CCPA 1967).

A specification must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, *i.e.*, whatever is now claimed. Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ.2d 1111, 1117 (Fed. Cir. 1991). A written description requirement issue generally involves the question of whether the subject matter of a claim is supported by or conforms to the disclosure of an application as filed. The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)) (see also, MPEP 2163.02).

An objective standard for determining compliance with the written description requirement is "does the description clearly allow persons of skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ.2d 1614, 1618 (Fed. Cir.1989).

The Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. In re Wertheim, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *See also* Ex parte Sorenson, 3 USPQ.2d 1462, 1463 (Bd. Pat.App. & Inter. 1987). By disclosing in a patent application a device that inherently performs a function or has a property, operates according to a theory or has an advantage, a patent application necessarily discloses that function, theory or advantage, even though it says nothing explicit concerning it. The application may later be amended to recite the function, theory or advantage without introducing prohibited new matter. In re Reynolds, 443 F.2d 384, 170 USPQ 94 (CCPA 1971); and In re Smythe, 480 F. 2d 1376, 178 USPQ 279 (CCPA 1973).

Furthermore, the subject matter of the claims need not be described literally (*i.e.*, using the same terms or *inhaec verba*) in order for the disclosure to satisfy the description requirement. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. This conclusion will result in the rejection of the claims affected under 35 U.S.C.112, first paragraph - description requirement, or denial of the benefit of the filing date of a previously filed application, as appropriate.

Analysis

The instant specification provides fusion proteins containing zinc finger peptide nucleotide binding domains operatively linked to ligand binding domains derived from an intracellular receptor that may further comprise an operatively linked transcription regulating domain. The specification provides extensive lists of examples of each domain and exemplifies preparation of various fusion proteins having the structural and functional limitations as claimed. There is nothing of record that suggest applicant did not contemplate a fusion protein containing a ligand binding domain derived from an intracellular receptor, a DNA binding domain that is a zinc finger peptide assembled from modular units that specifically recognize 3 nucleotide sequences, and a transcription regulation domain. Moreover, the specification clearly sets forth the types of variants in each domain that would satisfy the structural and functional limitations of the claims.

The specification exemplifies in great detail the construction and expression of the claimed fusion genes, assays that screen for variants that fall within the scope of the claims by measuring specific binding of each of the domains, and assays to measure their potential as regulators of gene expression. As discussed above, the classes of molecules belonging to each of the domains of the instantly claimed fusion proteins had been characterized in exquisite detail in the art as of the effective filing date of the instant application and have also been extensively

described in the specification so as to be adequately descriptive of "variants" that fall within the scope of the claims. Furthermore, as is well known to those of skill in the art (*see* above), and as described extensively in the specification, recombinant technology and binding assays may be uniformly applied to any or all of the molecules described in the specification due to their common structural and functional characteristics such as their target recognition sites, the structural motifs that create the specificity of recognition, and methods by which their ligand binding characteristics may be altered.

The ligand binding domain and variants thereof that would fall within the scope of the claims are described extensively at, for example, page 32, line 7 to page 33, line 11 of the specification, which provides methods, known to those of skill in the art, to prepare and characterize variants of the ligand binding domain, including specific changes that will provide altered endogenous or exogenous ligand specificity as desired. Page 33, line 12 to page 50, line 2 of the specification provides in exquisite detail and incorporates by reference what was known to those of skill in the art at the time of filing of the application concerning zinc finger proteins, the modular nature of zinc finger proteins wherein each zinc finger specifically recognizes a 3 nucleotide sequence, the types of zinc finger proteins, specific changes that provide variant zinc finger peptides that retain the characteristics of recognizing zinc finger DNA binding motifs, the rules for constructing, isolating or synthesizing such variants, and how to screen for such variants. Page 50, line 3 to page 52, line 5 of the specification describes known transcriptional regulatory domains and selection and modifications thereof. At, for example, page 31, line 6, to page 32, line 6, the specification describes how to construct the claimed fusion proteins from the various domains and their variants. In addition, numerous working examples, discussed above, are provided throughout the specification, as are exemplary fusion proteins, encoded by SEQ ID NOS. 1-18. As described above, the working examples also set forth in great detail the construction and screening of variants that fall within the scope of the instant claims

For eaxmple, Page 32, line 7 to page 33, line 11 of the specification states:

1. **Ligand Binding Domain (LBD)**

The ligand binding domain is derived from an intracellular receptor, and is preferably derived from a nuclear hormone receptor. The LBD of an intracellular receptor includes the approximately 300 amino acids from the carboxy terminal, which can be used with or without modification. By mutation of a small number of residues ligand specificity can be altered. The ligand binding domain can be modified, such as by truncation or point mutation to alter its ligand specificity permitting gene regulation by non-natural or non-native ligands.

Exemplary hormone receptors are steroid receptors, which are well known in the art. Exemplary and preferred steroid receptors include estrogen and progesterone receptors and variants thereof. Of particular interest are ligand binding domains that exhibit altered ligand specificity so that the LBD does not respond to the natural hormone, but rather to a drug, such as RU486, or other inducer. **Means to modify and test the specificity of ligand binding domains and to identify ligands therefor are known (see, U.S. Patent No. 5,874,534; U.S. Patent No. 5,935,934; and International PCT application No. 98/18925, which is based on U.S. provisional application Serial No. 60/029,964; International PCT application No. 96/40911, which is based on U.S. application Serial No. 08/479,913).**

The LBD can be modified by deletion of from about 1 up to about 150, typically 120, amino acids on the carboxyl terminal end of the receptor from which the LBD derives. Systematic deletion of amino acids and subsuqent testing of the ligand specificity and of the resulting LBD can be used to empirically identify mutations that lead to modified LBDs that have desired properties, such as preferential interaction with non-natural ligands. Exemplary mutations are described in the Examples herein, and also are known to those of skill in the art (see, *e.g.*, U.S. Patent No. 5,874,534; U.S. Patent No. 5,935,934; U.S. Patent No. 5,364,791; and International PCT application No. 98/18925, which is based on U.S. provisional application Serial No. 60/029,964; International PCT application No. 96/40911, which is based on U.S. application Serial No. 08/479,913l) and references cited therein. **Hence a LBD or modified form thereof prepared by known methods is obtained and operably linked to a DBD; a TRD is also linked as needed.** (emphasis added).

For example, at page 33, lines 15-29 of the specification:

Zinc fingers are ubiquitous proteins, and many are well-characterized. **For example, methods and rules for preparation and selection of zinc fingers based upon the C2H2 class of zinc fingers with unique specificity are known** (see, *e.g.*, International PCT application No. WO 98/54311 and International PCT application No. 95/19431; see, also U.S. Patent No. 5,789,538; Beerli *et al.* (1999) *Proc. Natl. Acad. Sci. U.S.A. 96*:2758-2763; Beerli *et al.* (1995) *Proc. Natl. Acad. Sci. U.S.A. 95*:14628-14633; see, also U.S. application Serial No. 09/173,941, filed 16 October, 1998, published as

> International PCT application No. WO 00/23464). Exemplary targeting sequences are provided herein.
> **Furthermore, other zinc fingers can be similarly identified and the rules known for the C2H2 can be applied to modification of the specificity of such zinc fingers or alternative rules unique to each class can be deduced in a similar manner**. (emphasis added).

Further, at page 34, lines 16-30:

> **For example, zinc finger variants can be prepared by identifying a zinc finger or modular unit thereof, creating an expression library, such as a phage display library** (see, *e.g.*, International PCT application No. WO 98/54311, Barbas *et al.* (1991) *Methods 2*:119; Barbas *et al.* (1992) *Proc. Natl. Acad. Sci. U.S.A. 89*:4457), encoding polypeptide variants of the zinc finger or modular unit therof, expressing the library in a host and screening for variant peptides having a desired specificity. Zinc fingers may also be constructed by combining amino acids (or encoding nucleic acids) according to the known rules of binding specificity and, if necessary, testing or screening the resulting peptides to ensure the peptide has a desired specificity. **Because of the modular nature of zinc fingers, where each module can be prepared to bind to three nucleotide squence, peptides of any specificity can be prepared from the modules.** The number of modules used depends upon the specificity of gene targeting desired. (emphasis added).

Example 1 at page 67 of the specification provides a number of zinc finger variants produced in the manner described throughout the specification.

Further, at page 50, lines 13-18 of the specification:

> **Selection of the TRD**
> Transcription regulating domains are well known in the art. Exemplary and preferred transcription repressor domains are ERD, KRAB, SID, Deacetylase, and derivatives, multimers and combinations thereof such as KRAB-ERD, SID-ERD, $(KRAB)_2$, $(KRAB)_3$, KRAB-A, $(KRAB\text{-}A)_2$, $(SID)_2$ (KRAB-A)-SID and SID-(KRAB-A).

Based on the knowledge of those of skill in the art at the time that the application was filed (*see* descriptions above), the specification fully describes the subject matter as claimed at the time that the application was filed. Furthermore, it must be noted that the Examples set forth standard technologies and specific structural features for the construction and assay of the fusion protein variants that fall within the scope of the claims.

Therefore, because there is extensive written description as to the identity, structural features, sequence variants, and screens to identify the sequence variants of the claimed fusion proteins, Applicant had possession of the claimed subject matter at the time of filing of the application.

THE REJECTION OF CLAIMS 1-35, 37-46 and 69-73 UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 1-35, 37-46 and 69-73 are rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that applicants regard as the invention. Various bases for this rejection are set forth and each is discussed in turn. Reconsideration of the grounds for rejection is respectfully requested in view of the amendments of the claims and the following remarks.

Relevant Law

Definiteness of claim language must be analyzed, not in a vacuum, but in light of (1) the content of the particular application disclosure, (2) the teachings of prior art, and (3) the interpretation claims would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made. Claims need only "reasonably apprise those skilled in the art" of their scope and be "as precise as the subject permits." Hybritech Inc. v. Monoclonal Antibodies, Inc., 231 USPQ 81, 94 (Fed. Cir. 1986), cert. den., 480 U.S. 947 (1987). The Court in Orthokinetics, Inc v. Safety Travel Chairs, Inc., 1 USPQ2d 1081 (Fed. Cir. 1986) held that a claim limitation requiring that a pediatric wheelchair part be "so dimensioned as to be insertable through the space between the doorframe of an automobile and one of the seats" is definite. The Court stated:

> The phrase 'so dimensioned' is as accurate as the subject matter permits, automobiles being of various sizes. As long as those of ordinary skill in the art realized that the dimensions could be easily obtained, § 112, 2d ¶ requires nothing more. The patent law does not require that all possible lengths corresponding to the spaces in hundreds of different automobiles be listed in the patent, let alone that they be listed in the claims.

1 USPQ2d at 1088.

When one skilled in the art would understand all of the language in the claims when read in light of the specification, a claim is not indefinite.

Applicant is unaware of any requirement that terms be defined in the claims when one of skill in the art can readily determine the meaning of the term based on the description and definitions provided in the specification. In this respect, applicant is entitled to be its own lexicographer [see, e.g., MPEP 2111.01 "Applicant may be his or her own lexicographer as long as the meaning assigned to the term is not repugnant to the term's well known usage and utilize terms within the claims that are clear from a reading of the specification]. In re Hill, 73 USPQ 482 (CCPA 1947)". When applicant has provided definitions in the specification, the claims are interpreted in light of such definition.

35 U.S.C. §112, second paragraph requires only reasonable precision in delineating the bounds of the claimed invention. The claim language is satisfactory if it reasonably apprises those of skill in the art of the bounds of the claimed invention and is as precise as the subject matter permits. Shatterproof Glass Corp.v. Libby-Owens Ford Col, 758 F.2d 613, 624, 225 USPQ 634, 641 (Fed. Cir), cert dismissed, 106 S. Ct. 340 (1985).

The amount of detail required to be included in the claims depends on the particular invention and the prior art and is not to be viewed in the abstract, but in conjunction with whether the specification is in compliance with the first paragraph of 35 U.S.C. §112. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more:

> [i]t is not necessary that a claim recite each and every element needed for the practical utilization of the claimed subject matter (Bendix Corp. v United States, 600 F.2d 1364, 1369, 220 Ct. Cl. 507,514, 204 USPQ 617, 621 (1979); See, also, Carl Zeiss Stiftung v. Renishaw plc, 20 USPQ2d 1094, 1101).

Analysis

1) The Examiner alleges that claims 4 and 5 are indefinite in their recitation of the term "derived from".

This rejection is rendered moot by cancellation of Claim 4. With respect to amended Claim 1, it is respectfully submitted that basis for the term "derived from" is found at page 15, lines 6-11 of the specification, which recites that the ligand binding domain is "derived from" the 300 amino acid carboxyl terminal half of intracellular receptors, and is the portion of the receptor protein with which a ligand interacts.

2) The Examiner alleges that claims 4, 5 and 13 are unclear in their recitation of the term "selectivity". This rejection is obviated with respect to claims 4 and 5 by cancellation of Claim 4.

With respect to Claim 13, this rejection is traversed. There is basis in the specification for the term selectivity as meaning an altered binding specificity relative to the native ligand binding domain, and methods of assaying for this selective preference is incorporated by reference in the specification at page 5, lines 5-20 (see, *e.g.*, U.S. Patent No. 5,874,534 and Wang *et al.* (1994) *Proc. Natl. Acad. Sci. U.S.A. 91*:8180-8184) and in Example 14 at page 113 of the specifiaction.

3) The Examiner alleges that claim 5 is indefinite in its recitation of the term "substantially". This rejection is obviated by amending the claim to recite "relative to exogenous or non-natural ligands". Basis for this amendment may be found, e.g., at page 5, lines 1-4 of the specification and at page 10, lines 23-26 of the specification.

4) The Examiner alleges that claims 1, 8 and 69 recite the term "specifically" which is indefinite. This rejection is respectfully traversed. "Specifically" is a term of art and the specification at *e.g.*, page 33, line 12 to page 34, line 15 provides basis, supported by publications incorporated by reference, for determining the specificity of binding of modular units of a zinc finger peptide that specifically interact with 3 nucleotide contiguous sequences. Also, e.g., page 39, lines 17-27 of the specification, and Example 1 at page 67 of

the specification provide in great detail how specific binding of zinc finger peptides to their recognition motifs is determined.

5) The Examiner alleges that Claim 21 is vague and indefinite in its recitation of the terms "KRAB-ERD", "SID-ERD", "$(KRAB)_2$", etc. This rejection is respectfully traversed. The specification at *e.g.*, page 51, lines 3-30 defines these proteins as ERF repressor domain (ERD) (Sgouras *et al.* (1995) *EMBO J. 14*:4781-4793), defined by amino acids 473 to 530 of the *ets2* repressor factor (ERF); Krüppel-associated box (KRAB) domain (Margolin *et al.* (1994) *Proc. Natl. Acad. Sci. USA 91*:4509-4513); mSIN3 interaction domain (SID); Deacetylase, and derivatives, multimers and combinations thereof (see also, *e.g.*, page 7, lines 24-29 of the specification).

6) The Examiner alleges that claims 1, 8, 69 and dependent claims 2-7, 9-46, 70-73 are rejected for recitation of the term "modular portion". This rejection is respectfully traversed. The specification provides in great detail that zinc finger proteins are modular proteins where each modular unit specifically recognizes a 3 nucleotide sequence, and that the nucleotide binding domains provided in the instant application are combinations of one or more such modules. See, e.g, page 5, line 29 to page 6, line 4; page 34, line 26 to page 36, line 4 of the specification.

THE REJECTION OF CLAIMS 1-19, 23, 24, 26-31 and 69-73 UNDER 35 U.S.C. § 102

Claims 1-19, 23, 24, 26-31 and 69-73 are rejected under 35 U.S.C. §102(b) as being anticipated by U.S. Patent No. 5,217,867 (Evans *et al.*). The Examiner alleges that Evans *et al.* discloses fusion polypeptides containing a zinc-finger domain from the thyroid hormone receptor with the transactivation domain of the glucocorticoid receptor (column 5, line 63 to column 6, line 7; and Figure 3); that the fusion protein has been altered such that its ligand selectivity is altered; that it is an inherent property of zinc finger proteins to bind to a (GNN)n sequence; and that the zinc finger domain could be considered a "variant" of a C2H2 modular unit. The Examiner further alleges that Evans *et al.* discloses the nucleic acid encoding the fusion proteins, host cells and vectors (column 16, lines 5-60) and the transfection of host cells with plasmids expressing the chimeric receptors; and

that binding of nuclear receptors to DNA is an inherent property. The Examiner concludes that Evans *et al.* anticipates the rejected claims.

Reconsideration and withdrawal of this rejection is respectfully requested in view of the amendments herein and the following remarks. It is respectfully submitted that this rejection has been rendered moot with respect to Claim 4, which has been cancelled.

Relevant law

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. In re Spada, 15 USPQ2d 1655 (Fed. Cir, 1990), In re Bond, 15 USPQ 1566 (Fed. Cir. 1990), Soundscriber Corp. v. U.S.. 360 F.2d 954, 148 USPQ 298, 301, adopted 149 USPQ 640 (Ct. Cl.) 1966. See, also, Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913,1920 (Fed. Cir.), cert. denied, 110 S.Ct. 154 (1989). "[A]ll limitations in the claims must be found in the reference, since the claims measure the invention". In re Lang, 644 F.2d 856, 862, 209 USPQ 288, 293 (CCPA 1981). Moreover it is incumbent on Examiner to id entify wherein each and every facet of the claimed invention is disclosed in the reference. Lindemann Maschinen-fabrik Gmbh v. American Hoist and Derrick Co., 730 F.2d 1452, 221 USPQ 481 (Fed. Cir. 1984).

Further, the reference must describe the invention as claimed sufficiently to have placed a person of ordinary skill in the art in possession of the invention. Prior art does not anticipate a thing or process unless it is enabling; an anticipatory publication must describe the claimed invention with sufficient clarity and specificity so that one skilled in the relevant art could practice the subject matter of the patent without assistance from the patent claimed to have been anticipated Columbia Broadcasting System v. Sylvania Elec. Products, Inc., 415 F.2d 719, 735, 162 USPQ 577 (1st Cir.1968) cert. denied, 396 U.S. 1061, 164 USPQ 321 (1970).

"Before any publication can amount to a statutory bar to the grant of a patent, its disclosure must be such that a skilled artisan could take its teachings in combination with his own knowledge of the particular art and be in possession of

the invention." Titanium Metals crp. v Mossinghoff, 603 F.Supp. 87,0, 225 USPQ 673 (1984) quoting In re Application of Le Grice 49 CCPA 1124, 301 F.2d 9333

The claims

Claim 1 is directed to a fusion protein containing a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, where the nucleotide binding domain is a polydactyl zinc finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides; the ligand binding domain is modified to change its ligand specificity compared to the native hormone receptor; and the fusion protein is a ligand activated transcriptional regulator. Claims 2, 3, 5-7 and 9-19, 23-24, 26-31 and 69-73 are all directed to Claim 1 or dependents thereof that specify various limitations of the elements of Claim 1 or dependents thereof, or further comprise a transcription regulating domain (Claim 2), or are directed to nucleic acid molecules encoding the fusion proteins of Claims 1 or 2, or to to vectors containing the sequence of nucleic acid molecules encoding the fusion proteins of Claims 1 or 2, to cells containing these vectors, or to non-viral delivery systems containing the fusion protein of Claim 1.

Claim 8 is directed to a fusion protein containing a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, where the nucleotide binding domain is a polydactyl zinc finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides; the zinc finger peptide contains C2H2 zinc-finger modular units that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides; and the fusion protein is a ligand activated transcriptional regulator.

Differences between the disclosure of Evans et al. and the claimed subject matter

Evans *et al.* is aimed at identifying and characterizing the transactivation domains of hormone receptors by generating hybrid receptors in which the transactivation domain of one receptor is linked to the ligand binding and DNA binding domains of another. The "hybrid receptors" are then screened for

augmented transactivation activity relative to the native receptors. Evans is aimed at identifying novel receptors having increased transcription trans-activation properties. The "hybrid receptors" disclosed in Evans *et al.* contain only combinations of various naturally occurring ligand and DNA-binding receptor domains in which an additional transactivation domain is inserted or otherwise modified, so that the transcriptional activity is increased. Evans *et al.* does not disclose any natural or hybrid receptors having modified ligand binding domains such that the ligand specificity of the ligand binding domain is modified relative to that in the native receptor. Contrary to the Examiner's assertion, the ligand-binding and DNA-binding domains of the receptors in Evans *et al.* retain their original ligand or sequence specificity of the ligand-binding and nucleotide binding domains in the presence of an added or otherwise modified transactivation domain (which is distinct from the ligand binding and DNA binding domains; see, *e.g.*, Col. 2, line 62 - Col. 3, line 27). Evans *et al.* does not disclose fusion proteins containing a nucleotide binding domain operatively linked to a ligand binding domain in which the ligand specificity (*i.e.*, preference for exogeneous or non-natural ligands over the natural ligands) of the ligand-binding domain is modified. Therefore, Evans does not anticipate Claims 1, 2, 3, 5-7, 9-19, 23-24, 26-31 and 69-73. Further, Evans does not disclose nucleotide binding domains containing modular units from the synthetic C2H2 zinc finger family; therefore Evams does not anticipate Claim 8.

Therefore, since anticipation requires that a reference teach all elements as claimed , Evans et al. does not anticipate any of the claims.

* * *

In view of the remarks herein, examination of on the merits is respectfully requested.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: **Barbas III et al.**

Serial No.: 09/586,625

Filed: June 2, 2000

For: **LIGAND ACTIVATED TRANSCRIPTIONAL REGULATOR PROTEINS**

Art Unit: 1646

Examiner: Murphy, J.

I hereby certify that this paper and the attached papers are being deposited with the United States Postal Service as first class mail in an envelope addressed to:

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08/08/02
Date

Stephanie Seidman

ATTACHMENTS TO RESPONSE TO OFFICE ACTION

1. Marked-up claims (37 C.F.R. § 1.121)

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MARKED UP CLAIMS (37 C.F.R. § 1.121)

Please amend claims 1, 5, 8, 13, 20, 22, 25, 32, 34, 39, 43 and 45 as follows:

1. (Amended) A fusion protein, comprising a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, wherein:

the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides; [and]

the ligand binding domain has been modified to change its ligand specificity compared to the native hormone receptor; and

the fusion protein is a ligand activated transcriptional regulator.

5. The fusion protein of claim [4] 1, wherein the modified ligand-binding domain is not substantially activated by endogenous ligands relative to exogenous or non-natural ligands.

8. (Amended twice) [The fusion protein of claim 1] A fusion protein, comprising a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, wherein:

the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide

the zinc-finger peptide is comprised of modular units from a C2H2 zinc-finger peptide [or a variant thereof] that specifically interacts with a sequence of nucleotides and targets the fusion protein to an exogenous or endogenous gene that comprises the sequence of nucleotides[.]; and

the fusion protein is a ligand activated transcriptional regulator.

13. The fusion protein of claim [4] 3, wherein the hormone receptor is a progesterone receptor variant or an estrogen receptor variant, wherein a receptor variant comprises a ligand binding domain that has selectivity and sensitivity for endogenous and exogenous ligands that differ from its native ligands.

20. (Amended) [The fusion protein of claim 2] A fusion protein, comprising a nucleotide binding domain operatively linked to a transcription regulating domain and a ligand binding domain derived from an intracellular receptor, wherein:

the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides;

the transcription regulating domain comprises a transcription repression domain; and

the fusion protein is a ligand activated transcriptional regulator.

22. (Amended) [The fusion protein of claim 2] A fusion protein, comprising a nucleotide binding domain operatively linked to a transcription regulating domain and a ligand binding domain derived from an intracellular receptor, wherein

the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides;

the fusion protein is a ligand activated transcriptional regulator; and the

25. (Amended twice) [The nucleic acid molecule of claim 23] A nucleic acid molecule, comprising a sequence of nucleotides encoding a fusion protein, wherein:

the fusion protein comprises a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, wherein the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides;

the fusion protein is a ligand activated transcriptional regulator; and

the fusion protein is encoded by a sequence of nucleotides set forth in any of SEQ ID Nos. 1-18.

32. (Amended) [The vector of claim 26 that is a] A viral vector comprising a sequence of nucleotides encoding a fusion protein, wherein:

the fusion protein comprises a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, wherein the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides; and

the fusion protein is a ligand activated transcriptional regulator.

34. (Amended) The vector of claim 32, wherein the viral vector is derived from a DNA virus or a retrovirus.

39. (Amended) A combination, comprising:

a fusion protein [of claim 1] comprising a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, wherein the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides and the fusion protein is a ligand activated transcriptional regulator; or

a nucleic acid molecule comprising a sequence of nucleotides that encodes the fusion protein; and

a regulatable expression cassette that comprises at least one response element recognized by the nucleic acid binding domain of the fusion protein.

43. (Amended) A composition for regulating gene expression, comprising [:] an effective amount of: [the]

a fusion protein [of claim 1] comprising a nucleotide binding domain operatively linked to a ligand binding domain derived from an intracellular receptor, wherein the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that specifically interacts with a contiguous nucleotide sequence of at least about 3 nucleotides and the fusion protein is a ligand activated transcriptional regulator; or

a nucleic acid molecule comprising a sequence of nucleotides that encodes the fusion protein; and

a pharmaceutically acceptable excipient.

45. (Amended) A composition for regulating gene expression comprising[:] an effective amount of: [the]

a fusion protein [of claim 2] comprising a nucleotide binding domain operatively linked to a transcription regulating domain and a ligand binding domain derived from an intracellular receptor, wherein the nucleotide binding domain is a polydactyl zinc-finger peptide or modular portion thereof that